

Consumption of antibiotics in Greenland, 1964-70

IV. Changes in the sensitivity of N. gonorrhoeae to antibiotics

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The selection of strains of gonococci with reduced sensitivity to a drug is considered to be due to the presence of subinhibitory concentrations of antibiotics at the site of infection. The possibility of limiting this selection has been reported in numerous publications. Interest has been centred in the failure rates of various drugs used in the treatment of gonorrhoea, in the rate at which the drugs are eliminated from the body, and in the prevalence of inadequate self-medication. The coincidental effects of antibiotics used to treat other conditions on coexistent but unrecognized gonorrhoeal infections and consequently on the resistance pattern of the gonococci have not been investigated.

A survey of drug consumption in Greenland from 1964 to 1970 (Olsen, 1973a) has enabled an evaluation to be made of the possible effect of antibiotics on unrecognized gonorrhoea (Olsen, 1973b).

Publichealth conditions in Greenland are favourable for such an assessment for the following reasons:

(1) The treatment of gonorrhoea since 1964 (Olsen and Lomholt, 1969) has proved to be almost 100 per cent. effective; this fact has also been confirmed by Gray, Phillips, and Nicol (1970) and Niordson and Ullman (1971).

(2) After such treatment, the penicillin is rapidly eliminated about 8 hours after the concentration in the serum has fallen below curative levels (Schmidt and Roholt, 1966). Thus the risk of re-infection before all the penicillin has been eliminated is limited.

(3) There are few opportunities for self-medication in Greenland, since medicines are supplied only on prescription by the doctor (or the local midwife, if the doctor is not available).

(4) Prophylactic treatment with long-acting peni-

cillins has not been used in Greenland since 1963.

(5) The relative isolation of Greenland means that fewer strains of gonococci with reduced sensitivity are imported (Möller, 1971; Wols-van der Wielen, 1971), although during the summer and autumn months infection may spread along the coast.

The effects of subinhibitory concentrations of drugs on strains of gonococci are thus limited mainly to cases in which the drugs are given to persons with unrecognized gonorrhoea in amounts too small to eradicate the gonococci.

The sensitivity of gonococci to antibiotics in Greenland has been described by Reyn (1962), who found that 10 per cent. of the strains from Godthaab in 1960-61 were less sensitive to penicillin. In 1962, the frequency had risen to 86 per cent. (Boggild, 1965) and Lomholt and Berg (1966) considered that this was due to the use of the long-acting benzathine penicillin for the treatment of gonorrhoea. Furthermore, Boggild (1965) found that 42 per cent. of the strains had reduced sensitivity to tetracycline. Olsen and Lomholt (1969) reported on the resistance of strains from the town of Julianehaab from 1964 to 1967, and showed that those with reduced sensitivity to penicillin fell from 54 per cent. in 1964-65 to 19 per cent. in 1966-67. The greater sensitivity to penicillin seemed to be related to the introduction of a more effective treatment for gonorrhoea in the area, but further details were not given. The varying influence of drug treatment on the resistance pattern of gonococci in Greenland will be examined in the present paper.

Material and methods

(a) 4,023 strains of gonococci were received at the Gonococcus Laboratory in Julianehaab from June, 1964, to March, 1970; they originated from the districts

TABLE I Sensitivity determinations performed at *Gonococcus* Laboratory, Julianehaab, 1964 to 1970, by place of origin and year

Year		1964	1965	1966	1967	1968	1969	1970	Total
Frederikshaab	Town	5	27	82	180	61	8	—	363
	Settlements	2	—	1	6	1	—	—	10
Julianehaab	Town	129	178	311	377	185	174	103	1457
	Settlements	90	103	103	115	56	41	18	526
Narssak	Town	83	137	273	235	126	78	30	962
	Settlements	6	3	2	2	1	3	5	22
Nanortalik	Town	117	98	109	167	56	40	9	596
	Settlements	2	12	2	64	7	—	—	87
Total		434	558	883	1146	493 ^a	344	165	4023

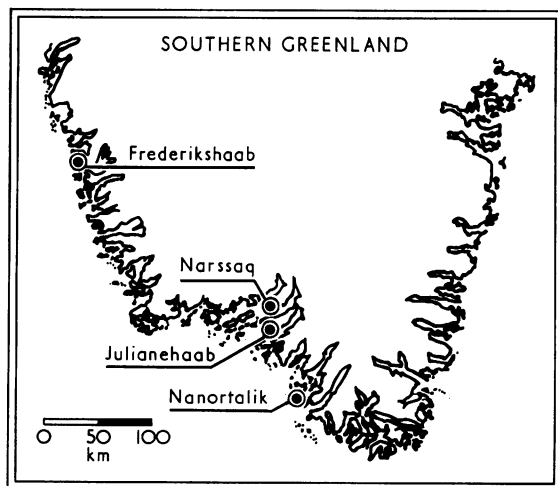
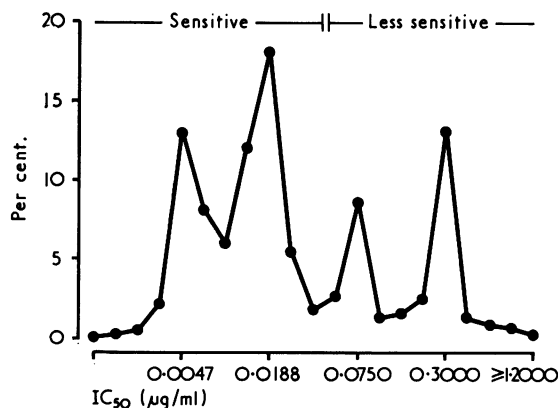
^aSensitivity determinations not performed in July quarter

FIG. 1 Map of Southern Greenland

shown in Fig. 1 and were distributed according to the forwarding centres shown in Table I.

Sensitivities were determined on all strains isolated from the opening of the laboratory in 1964 until June, 1968. From October, 1968, up to and including the first quarter of 1970, three-quarters of the unselected strains were examined. In January, 1971, 121 strains were sent to the Neisseria Department of the Statens Seruminstitut, Copenhagen, for sensitivity determinations. These are not included in the series, but will be briefly mentioned.

- (b) The method used was the plate-dilution technique of Reyn, Bentzon, and Ericsson (1963). The 50 per cent. inhibitory antibiotic concentration was used to indicate sensitivity *in vitro* (IC_{50} μ g./ml.). For streptomycin, the strains are merely designated sensitive or resistant. Sodium benzylpenicillin, tetracycline hydrochloride, and dihydrostreptomycin sulphate were used in the examinations *in vitro*.

FIG. 2 Distribution of IC_{50} values for penicillin in Southern Greenland, 1964 to 1970

Results

PENICILLIN

The distribution of the strains according to their sensitivity to penicillin *in vitro* is shown in Fig. 2. One-third (32.7 per cent.) of the strains had reduced sensitivity to penicillin ($IC_{50} \geq 0.053$ μ g./ml.). In 0.3 per cent. the IC_{50} was ≥ 1.20 μ g./ml. There is some accumulation around the IC_{50} values 0.0047, 0.0188, 0.075, and 0.30 μ g./ml. This may be due to bias in the reading procedure, *i.e.* a tendency to neglect growth ranges 2 and 3 and to use only ranges 4 and 0 (See Reyn and others, 1963). The detailed distribution of the sensitivities in individual years is shown in Table II.

In Fig. 3 the strains are grouped according to their sensitivity to penicillin. The groups in the columns indicate the percentage frequency of such strains in the year in question; the values for 1970 are adjusted (see below). The frequency of the most

TABLE II Sensitivity to penicillin; IC_{50} values from 1964 to 1970

IC_{50} $\mu\text{g./ml.}$	1964	1965	1966	1967	1968	1969	1970
≤ 0.0012	2	—	—	—	—	—	—
0.0017	—	—	—	—	—	1	6
0.0024	—	2	12	—	—	1	1
0.0033	1	9	44	18	—	2	11
0.0047	20	60	160	145	59	33	45
0.0066	22	28	111	102	38	19	5
0.0094	29	27	67	78	25	8	3
0.0133	57	25	103	205	66	26	1
0.0188	73	62	164	258	142	29	3
0.027	8	7	72	112	15	4	2
0.038	7	31	15	18	3	2	2
0.053	18	39	11	27	4	4	2
0.075	83	128	22	60	38	12	3
0.106	11	24	5	1	4	9	—
0.150	11	30	16	6	1	4	—
0.21	15	25	19	10	7	22	2
0.30	41	48	56	94	82	132	73
0.42	7	7	3	7	4	16	3
0.60	10	4	2	4	3	9	1
0.85	14	1	1	—	2	9	—
≥ 1.20	5	1	—	1	—	2	2
Total	434	558	883	1146	493	344	165

sensitive strains is marked in the lower part of the columns. The circles show the annual frequency of sensitive strains, and the dotted areas those with reduced sensitivity. In 1964 and 1965, about 50 per cent. were sensitive and in 1969 and 1970 about 40 per cent., whereas there were 70 per cent. or more in 1966–68. A comparison of the first and last years of the period shows that the total numbers of strains with reduced sensitivity were similar, but that a marked change occurred in the frequency of the strains with the lowest sensitivities ($IC_{50} \geq 0.3$ $\mu\text{g./ml.}$), the percentages being more than 50 per cent. in 1969–70, less than 20 per cent. in 1964–65, and even less in 1966–67.

A seasonal variation was seen in the frequency of strains with reduced sensitivity (Table III). Only strains from the whole years in the experimental period are included. Less sensitive strains were most frequent in the July quarter, and least frequent in the January and April quarters. Since the strains from 1970 include only the January quarter, the 1970 column in Fig. 3 has been corrected by the deviation

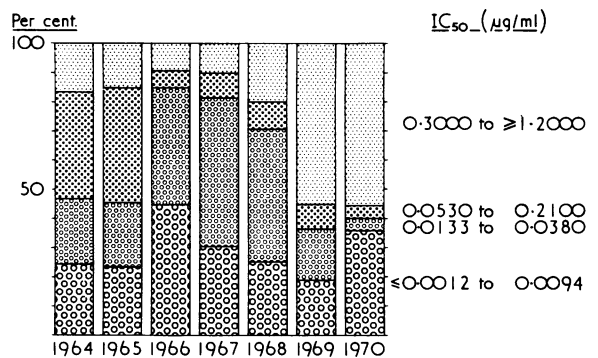


FIG. 3 Annual distribution of sensitivity of gonococci to penicillin in vitro, Southern Greenland, 1964 to 1970. January quarter 1970 corrected for seasonal variation

of the January quarters in 1965–69 from the average.

Fig. 4 (overleaf) shows the frequency of strains with reduced sensitivity in the towns and settlements in

TABLE III Seasonal variation in strains less sensitive to penicillin, 1965 to 1969

Year	No. of sensitivity determinations					No. of less sensitive strains					Percentage less sensitive strains				
	Quarter					Quarter					Quarter				
	1	2	3	4	Total	1	2	3	4	Total	1	2	3	4	Total
1965	212	167	112	67	558	114	85	83	25	307	53.8	50.9	74.1	37.3	55.0
1966	317	37	203	326	883	42	2	52	39	135	13.2	5.4	25.6	12.0	15.3
1967	278	140	392	336	1146	20	13	117	59	209	7.2	9.3	29.8	17.5	18.2
1968	221	202	—	70	493	68	42	—	35	145	30.8	20.8	—	50.0	29.4
1969	100	13	61	170	344	55	8	40	116	219	55.0	61.5	65.6	68.2	63.6
Mean											32.0	29.6	48.8	37.0	36.3

— = sensitivity determinations not performed in this quarter

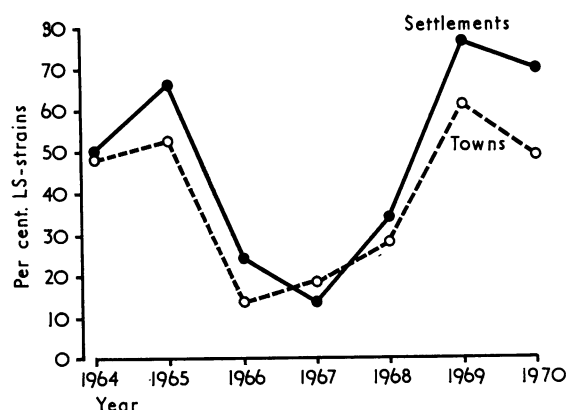


FIG. 4 Annual distribution of strains less sensitive to penicillin in towns and settlements

the area. The variations are fairly similar in the two areas, except that there are more strains with reduced sensitivity in the settlements in 1967. The values for the whole period are 31.6 per cent. of strains from the towns and 39.0 per cent. of strains from the settlements. Only a few of the strains from Frederikshaab derive from the settlements and the frequency of less sensitive strains in this centre differs from that of other centres in the area. In the geographically connected districts (Julianehaab, Narssak, Nanortalik), there was a significantly higher frequency of less sensitive strains in the settlements in 1965 and 1966.

A comparison was made between the sensitivity of strains from known pairs of contacts from Julianehaab in two selected periods (1st and 2nd quarters of 1967 and 1968). The results are shown in Fig. 5. The values for the contact pairs where the sensitivity was identical are plotted on the continuous line. The points above the line indicate the pairs in which the male's strain was less sensitive, and those below the line the pairs in which the female's strain was less sensitive. The two parallel broken lines show the 'permissible limits' outside which the contact pair in question can be regarded as a 'false pair', in accordance with the calculations of Schmidt and

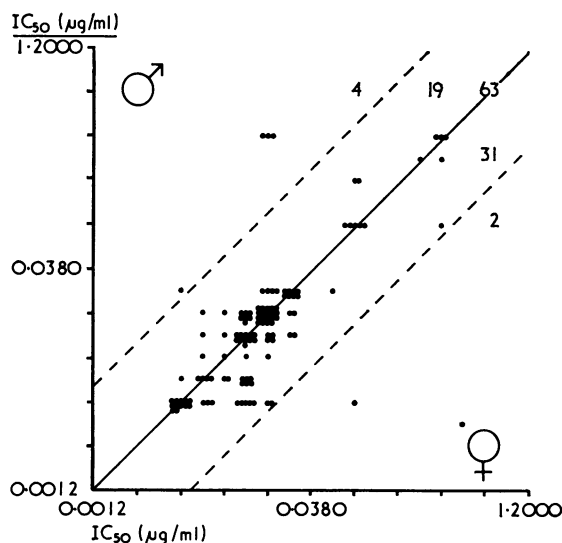


FIG. 5 Penicillin sensitivity of gonococcal strains isolated from 119 contact pairs. IC_{50} values

Olesen Larsen (1962). The strains from 53 per cent. of the pairs have identical sensitivities, 16 per cent. lie above this line, and 26 per cent. below but within the permissible limits. The female's strain was more often the less sensitive in both periods. The same tendency was seen by Schmidt and Olesen Larsen (1962). Taking all three observations into consideration, this tendency was significant.

STREPTOMYCIN

During the whole experimental period, 6.4 per cent. of strains were found to be resistant to streptomycin, but there were considerable variations from year to year and also between towns and settlements (Table IV). In 1964 and 1965, one-third to one-fourth of strains from the settlements and one-sixth to one-tenth of strains from the towns were resistant. The frequency of resistant strains was significantly higher in the settlements than in the towns in the Julianehaab, Narssak, and Nanortalik districts from 1964 to 1967. During subsequent years the frequency of

TABLE IV Annual distribution of strains resistant to streptomycin in towns and settlements

Year		1964	1965	1966	1967	1968	1969	1970
Towns	No.	31	73	22	10	7	14	19
	Per cent.	9.2	16.4	2.8	1.0	1.6	4.6	12.9
Settlements	No.	25	38	10	10	0	0	0
	Per cent.	25.8	33.0	9.4	5.4	—	—	—
Total	No.	56	111	32	20	7	14	19
	Per cent.	13.0	19.9	3.7	1.7	1.4	4.1	11.5

resistant strains declined; they re-appeared in the towns in 1969-70 but not in the settlements. Among the 121 strains examined in January-February, 1971, 24 per cent. were resistant. It is not known whether any of these originated from the settlements. No definite seasonal variation could be demonstrated.

TETRACYCLINE

The distribution of sensitivity to tetracycline is seen in Fig. 6, which shows that 2.5 per cent. of strains had reduced sensitivity ($IC_{50} \geq 1.13 \mu\text{g./ml.}$).

Fig. 7 shows the annual distribution of the strains according to their sensitivity. The less sensitive strains are shown at the top of the columns, and below them the sensitive strains are divided into three subsections, the lowest being the most sensitive. Strains with reduced sensitivity to tetracycline were found mainly in 1964 and 1965, when they comprised 13.4 and 6.1 per cent. of the total. From 1966 to

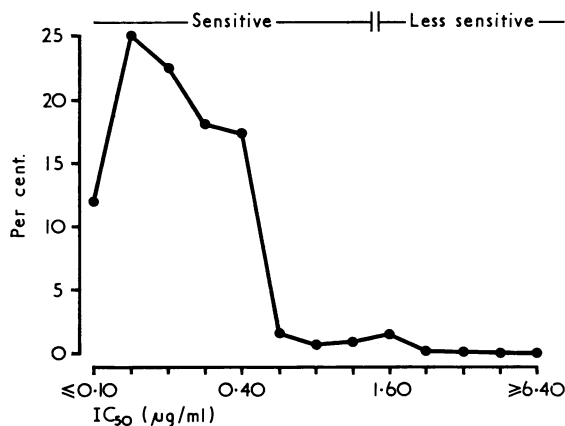


FIG. 6 Distribution of IC_{50} values for tetracycline in Southern Greenland, 1964 to 1970

TABLE V Percentage annual distribution according to sensitivity of strains isolated from 1964 to 1970 (1971) in Southern Greenland and in 1970 in Denmark (Reyn, 1971)

Year	Greenland							Denmark	
	1964	1965	1966	1967	1968	1969	1970	Jan. 1971	1970
Penicillin less sensitive strains	49.5	55.0	15.3	18.3	29.4	63.7	52.1	56.2	30.0
Streptomycin resistant	13.0	19.9	3.7	1.7	1.4	4.1	11.5	24.0	21.6
Percentage streptomycin resistant among penicillin less sensitive strains	26.0	34.2	21.5	7.1	4.8	5.0	18.4	41.2	71.8
Tetracycline less sensitive	13.4	6.1	0.5	0.1	0.2	0.3	—	5.8	11.4
Percentage tetracycline resistant among penicillin less sensitive strains	26.0	9.4	1.5	0.5	0.7	0.5	—	10.3	38.1
Multi-resistant	6.5	2.7	0.2	0.1	0.2	0.3	0.0	4.1	10.5

*Strains less sensitive to penicillin and tetracycline and resistant to streptomycin

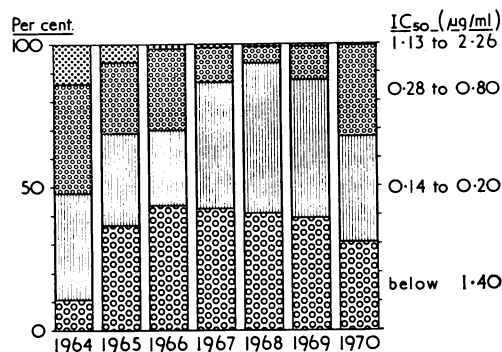


FIG. 7 Annual distribution of sensitivity of gonococci to tetracycline in vitro, Southern Greenland, 1964 to 1970

1970, only up to 0.5 per cent. were less sensitive. Thus, in contrast to the findings with penicillin and streptomycin, there was no increase in the frequency of strains with reduced sensitivity to tetracycline at the end of the period, but the particularly sensitive strains (IC_{50} values of $< 0.28 \mu\text{g./ml.}$) decreased again after 1968.

Nevertheless, the change in sensitivity to tetracycline was less pronounced than that to penicillin and streptomycin. In January-February, 1971, 6 per cent. of strains were less sensitive to tetracycline. No seasonal variations could be demonstrated, and there was no difference between the strains isolated in the towns and in the settlements.

MULTIRESISTANT STRAINS

The relationship between the sensitivities to penicillin, streptomycin, and tetracycline are given in Table V, which also shows the variations in the resistance patterns from year to year. The frequency of 'double' and 'multiresistant' strains decreased from 1964 to 1969. The numbers of strains less sensitive to both

penicillin and streptomycin were low in 1967-69, but increased again in the January quarter of 1970, and the tendency seemed to continue in 1971, when the position was similar for strains less sensitive to both penicillin and tetracycline. More 'multiresistant' strains were observed again in 1971, after having been very rare from 1966 to the January quarter of 1970.

Discussion

Theoretically, the selection of strains of gonococci with reduced sensitivity to antibiotics should be limited in Greenland to those caused by coincidental treatment of unrecognized cases of gonorrhoea. The following factors are of importance in this connection:

- (1) Antibiotic usage;
- (2) Changes in the prevalence of gonorrhoea;
- (3) Duration of infection.

The changes in the resistance pattern of the gonococci occurred in close temporal relationship to the start, the continuation, and the conclusion of the intensified campaign against gonorrhoea (Olsen, 1973c). From the middle of 1965 to the middle of 1968, the campaign halved the number of cases of gonorrhoea in the groups examined, and resulted in a 25-30 per cent. reduction of infections in the unmarried population as a whole, as compared to the previous and subsequent 4-year periods. Furthermore, during the intensified campaign, the infections with gonorrhoea could be expected to be of shorter duration than in the years before and after. The duration of the gonorrhoeal infection influences the failure rate with a given drug treatment (Olsen, 1973b). Besides limiting the chances of fortuitous exposure of gonococcal strains to a non-curative dosage, the shorter duration of an infection before treatment would result in a lower failure rate and thus further reduce the possibility of a selective effect on the sensitivity of the gonococci.

If the same type of treatment is prescribed more often, the possibility of coincidental selection is increased, whereas the failure rate is not immediately affected. If the intensity of the treatment is changed so that the serum concentrations are increased, the failure rate will be reduced. In that event, however, a subcurative dosage will result in the selection of strains with even less sensitivity.

The consumption of antibiotics which have an effect on the gonococcus doubled in Greenland (including the examination area) from 1964 to 1970 (Olsen, 1973a), partly because of an extension of the indications for drug treatment, and partly because of a gradual increase in the daily dosage.

Fig. 3 shows that it was particularly the strains with moderately reduced sensitivity to penicillin which decreased in frequency from 1965 to 1966. This may be because coincidental selective drug effects, occurring in cases in which the infection was of shorter duration, would cure infections caused by strains with moderately reduced sensitivity. As a consequence of the intensified campaign against gonorrhoea, the limiting effect on the duration of gonorrhoeal infections was maintained until the middle of 1968, when the mass campaign ended. However, the frequency of the strains most resistant to penicillin increased twofold from 1966 to 1968. This was presumably because the constantly more frequent and particularly more intensive drug treatment led to the selection of strains with further reduced sensitivity. This was especially evident after the conclusion of the mass examinations in 1968.

A 50 per cent. higher frequency of reactive gonococcal complement-fixation reactions was demonstrated in the settlements than in the towns in South Greenland (Olsen, 1965). This may be an indication that in the settlements gonorrhoeal infections were often of longer duration before treatment could be instituted. This agrees with the fact that strains with reduced sensitivity to penicillin were often particularly frequent in the settlements (Fig. 4). The longer duration of gonorrhoeal infections in females before treatment also involved a greater risk of a non-curative drug effect on the disease. This may be the reason why strains with reduced sensitivity to penicillin were isolated more frequently from females than from males in the contact pairs examined (Fig. 5). Correspondingly, Verhagen, van der Ham, Heimans, Kranendonk, and Maina (1971) demonstrated the highest proportion of less sensitive strains in the remote rural areas in Kenya.

Seasonal variations in the frequency of strains with reduced sensitivity to penicillin in Greenland correspond to those reported from North Sweden (Danielsson, 1971). Strains with reduced sensitivity were particularly frequent in the July quarter, whereas notified bacterial infections, and presumably also drug treatments, were more frequent in the October quarter (Olsen, 1973a). This may be because the heavier traffic in the ice-free summer and autumn months leads to an increased importation of less sensitive strains from the northerly coastal districts, thus masking the effect of antibiotic treatment in South Greenland. No seasonal variations in the sensitivity of gonococci to penicillin were demonstrated in Denmark (Reyn, 1969).

At the beginning of the examination period, streptomycin-resistant strains were found most frequently in the settlements. This was presumably because

both streptomycin and penicillin were used in the treatment of gonorrhoea in the settlements, whereas only penicillin was used in the towns (Gerdes, 1964). All the streptomycin-resistant strains found in 1969 and 1970 came from the towns, and there were none from Nanortalik, the most isolated town from the traffic point of view. This may also be interpreted as an indication of the importation of resistant strains from the northerly parts of the coast (Boggild, 1965).

The changes in the sensitivity to tetracycline at the beginning of the study period operated in the reverse direction to those for penicillin and streptomycin. In the later part of the period, the sensitivity to tetracycline changed less than the sensitivity to penicillin, even though the use of tetracycline increased more than that of penicillin in the same period (Olsen, 1973a). The selection of less sensitive strains might be expected to be more frequent in cases treated with tetracycline because of the slower elimination of the drug. That the opposite seems to be the case may be due to the higher cure rate of gonorrhoeal infections with the doses of tetracycline in general use, so that the chance of selection is less with tetracycline than with penicillin. Willcox (1968) reported that strains of gonococci with reduced sensitivity to tetracycline had appeared slowly, but he thought that was because the drug arrived later and was used less than penicillin. However, this opinion is not supported by the results of the present study.

In agreement with the findings of Reyn, Korner, and Bentzon (1958), Thayer, Samuels, Martin, and Lucas (1964), and others, the present study showed a positive correlation between the sensitivity to penicillin and that to streptomycin and tetracycline (Table V), but the resemblance is not so marked to the findings of Reyn (1961, 1971) in Denmark where there were no 'multiresistant' strains in 1960, but 10.5 per cent. in 1970. In Greenland, the frequency of 'multiresistant' strains declined from 1964 to 1970.

The relationship of our results to the mass campaign against gonorrhoea and to the increased use of antibiotics with an effect on the gonococcus during the examination period, suggests that variations in the sensitivity of the gonococcus, particularly to penicillin, may be explained by the varying possibilities for selection of less sensitive strains caused by a coincidental drug effect ('happenstance effect') on unrecognized gonorrhoeal infections.

This relationship between drug consumption and the sensitivity of gonococcal strains is to be expected in Greenland, partly because of the public health conditions and the relative isolation of the country.

The 'happenstance effect' of drug treatment on gonorrhoeal infection may be expected to be global,

but differences in facilities for treatment and in drug consumption will result in differences in the local resistance pattern, which also will be influenced by variations in the traffic pattern (Verhagen and others, 1971; Möller, 1971). Such factors will limit the opportunity of evaluating how far local drug usage may bring about unfavourable changes in the resistance pattern of the gonococcus.

Conclusions

In addition to the obvious need for a high cure rate in the treatment of gonorrhoea, adverse changes in the sensitivity of gonococci to antibiotics can be counteracted by limiting the other possibilities for selective antibiotic effects on these infections, as practised in prophylactic measures against this occurrence in hospital infections.

(1) Efforts should be made to limit the pool of undiagnosed gonorrhoeal infections by:

- (a) Effective tracing of contacts;
 - (b) Screening for cases of gonorrhoea in groups at high risk;
 - (c) Education of the public about venereal diseases.
- (2) Antibiotic treatment for other conditions should also be suitable for curing unrecognized gonorrhoeal infections. This requires a knowledge of the sensitivity of the gonococcal strains in the area.
- (3) The indications for antibiotic treatment in the area should be critically reviewed.

Summary

An account is given of the sensitivity *in vitro* to penicillin, streptomycin, and tetracycline of 4,023 strains of gonococci isolated and examined in Southern Greenland from 1964 to 1970. In close temporal relationship to the beginning and end of prophylactic mass screening of groups particularly exposed to gonorrhoeal infections, an increasing sensitivity of strains of gonococci in the district was observed at first, and this was followed by decreasing sensitivity, especially to penicillin.

Changes in the sensitivity of gonococci are presumably due mainly to variations in the exposure of gonorrhoeal infections to sub-curative treatment. Because of the shorter duration of gonorrhoeal infections from 1965 to 1968, there was less chance of exposure to the effect of 'happenstance treatment' in the same period. Furthermore, the higher cure rate meant that there was less likelihood that less sensitive strains would be selected than during the rest of the period studied.

The increasing frequency of antibiotic treatment and the larger daily doses used in Greenland are

likely to increase the chances of a 'happenstance effect' on unrecognized gonorrhoeal infections and thus to result in further selection of even less sensitive gonococcal strains.

The fact that this 'happenstance effect' has led to such unfavourable developments in the sensitivity of gonococci in Greenland must be considered against the background of the difficult living conditions in the area, which are associated with a higher frequency of non-venereal bacterial infections requiring antibiotic treatment. The limited facilities for an effective venereological service in Greenland result in a larger pool of undiagnosed cases of gonorrhoea than, for instance, in Denmark, so that a coincidental drug effect will probably lead more frequently to the selection of less sensitive strains of gonococci.

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Consommation des antibiotiques au Groënland en 1964-1970

SOMMAIRE

I. Considérations économiques et épidémiologiques

Dans une communauté, les facteurs épidémiologiques, socio-économiques et hygiéniques sont d'une importance primordiale pour déterminer la nécessité du traitement par les antibiotiques. Les ressources économiques et l'organisation des services médicaux ont une influence sur la consommation des médicaments. L'incidence relativement élevée des infections bactériennes au Groënland, le service de santé gratuit et la gratuité des médicaments fait que plus de médicaments y sont utilisés qu'au Danemark où le niveau de l'hygiène est plus élevé. L'emploi des antibiotiques au Groënland a augmenté de 70 à 80 pour cent entre 1964 et 1970 et la dépense par personne fut, en 1970, de 6,2 dollars US. L'importance de la consommation médicamenteuse et les facilités limitées du diagnostic bactériologique font qu'il est possible qu'une coïncidence d'effet sur des infections concomitantes non reconnues soit fréquente.

L'emploi des antibiotiques augmente dans le monde entier à des taux qui varient selon les conditions locales. Ceci parce que ces médicaments sont utilisés pour traiter beaucoup plus de maladies et que la posologie totale par traitement a augmenté d'une manière marquée. L'aspect de la consommation d'antibiotiques au Groënland a suivi la même voie que dans d'autres régions. Le traitement buccal est employé plus fréquemment que l'administration parentérale. Du point de vue bactériologique, la tendance à employer davantage d'antibiotiques à large spectre, tels que la tétracycline ou l'ampicilline, est regrettable.

Il est d'une importance épidémiologique, bactériologique et économique d'étudier l'emploi des médicaments dans une communauté et d'apprécier l'importance des traitements de coïncidence. Il est nécessaire aussi d'établir si, du point de vue médical, la dépense est justifiée par rapport à l'usage que l'on pourrait faire du même budget pour d'autres buts de santé publique.

II. Effet de l'administration d'antibiotiques par coïncidence dans la syphilis récente

Treponema pallidum est sensible aux antibiotiques les plus courants. Comme la consommation de ces drogues augmente à l'échelle mondiale, on peut s'attendre à plus d'effet par coïncidence sur les infections syphilitiques non reconnues.

Le traitement par la pénicilline de la gonococcie et d'autres maladies est plus à même la fois de guérir et de limiter l'extension de l'infection en cas de syphilis récente que lorsque l'on emploie la tétracycline qui peut seulement modifier de tels cas. Cependant, des

infections modifiées peuvent aussi être rencontrées après le traitement de la gonococcie par la pénicilline ou l'ampicilline lorsque l'on ne dispose pas de preuves cliniques ou sérologiques d'une infection récente, ce qui est susceptible de survenir dans les régions où les facilités médicales sont limitées. Ainsi, en ce qui regarde l'incidence de la syphilis reconnue dans une région et l'occurrence d'infections syphilitiques modifiées par l'emploi d'antibiotiques, la quantité et la variété des antibiotiques employés, les changements dans leur usage et l'état des facilités médicales disponibles, peuvent avoir une grande conséquence.

L'effet cumulatif d'un emploi largement répandu des antibiotiques sur l'infériorité des cas de syphilis récente a probablement entraîné une réduction de plus de 50 pour cent de ces cas au Danemark. Au Groënland, l'emploi plus fréquent des antibiotiques—spécialement dans la gonococcie—a entraîné des effets de coïncidence probablement plus grands qu'au Danemark sur l'incidence de la syphilis.

III. Effets de l'administration d'antibiotiques par coïncidence dans les affections gonococciques

Sur la base de la consommation d'antibiotiques au Groënland, on a estimé l'effet de coïncidence d'un traitement antibiotique sur les infections gonococciques non reconnues. Les résultats dépendent de la posologie et de la durée du traitement, de la sensibilité des souches aux médicaments employés et à la durée de l'infection. Le risque qu'un traitement antibiotique par coïncidence puisse entraîner une incidence accrue de souches de gonocoques de sensibilité réduite est donc plus grande là où le profil de la résistance est défavorable et où les mesures de santé publique pour suivre la diffusion des maladies vénériennes sont limitées.

La durée minimale d'une concentration sérique appropriée de la pénicilline pour avoir un effet curateur est probablement inférieure à 6 heures dans les infections gonococciques non compliquées n'ayant duré que peu de temps.

IV. Changement dans la sensibilité de *Neisseria gonorrhoeae* aux antibiotiques

On passe en revue la sensibilité *in vitro* à pénicilline, streptomycine et tétracycline de 4.023 souches de gonocoques isolées et examinées dans le Sud du Groënland de 1964 à 1970. En relation étroite dans le temps entre le début et la fin d'examen prophylactiques de masse de groupes particulièrement exposés aux infections gonococciques, on a d'abord observé une sensibilité accrue des souches de gonocoques dans le district considéré, suite par une diminution de cette sensibilité, spécialement vis-à-vis de la pénicilline.

Les changements dans la sensibilité des gonocoques sont probablement dus, principalement, aux variations du risque de traitement des infections gonococciques par des doses subcuratives. A cause de la durée plus courte des infections gonococciques entre 1965 et 1968, les occasions furent moindres pendant cette période d'un risque d'effet d'un 'traitement accidentel'. En outre, le plus haut taux de guérison veut dire qu'il y avait moins de risque de sélection de souches moins sensibles que pendant le reste de la période étudiée.

L'augmentation de la fréquence d'un traitement antibiotique et les doses journalières plus élevées employées au Groënland sont susceptibles d'augmenter les risques d'un 'traitement accidentel' sur les infections gonococciques non reconnues et, ainsi, d'aboutir à une sélection plus grande de souches de gonocoques encore moins sensibles.

Le fait que ce 'traitement accidentel' a entraîné un tel développement défavorable dans la sensibilité de gonocoques au Groënland doit être considéré par rapport aux difficiles conditions de vie dans cette région qui vont de pair avec une plus grande fréquence d'infections bactériennes non vénériennes obligeant à un traitement antibiotique.

Les facilités limitées d'un service vénéréologique efficace au Groënland a pour résultat de favoriser l'existence d'un réservoir plus grand de cas non diagnostiqués de gonococcie que, par exemple, au Danemark, si bien qu'un effet médicamenteux de coïncidence conduira probablement à une plus grande fréquence de sélection de souches moins sensibles de gonocoques.